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Polychlorinated Biphenyls, Organochlorines & PD Risk: A Case Control Study in Alaska

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None

14. ABSTRACT

The intent of this proposal is to conduct a case-control study of Parkinson's disease (PD) among Alaska Natives to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interview, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 is a developmental period and is complete for study conduct in Anchorage. The specific aspects of the study design were established, detailed protocols were developed, and the necessary Institutional Review Board (IRB) approvals for the research were obtained. Further approval is required for conduct outside of Anchorage. Phase 2, conduct of the case-control study, is now in progress in Anchorage.

15. SUBJECT TERMS
Parkinson's disease, Polychlorinated biphenyl, Organochlorine pesticides, Methylmercury, Alaska Natives, Neurodegeneration

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A. Introduction

The intent of this proposal is to conduct a case control study of Parkinson's disease (PD) among Alaska Native people to determine the association of exposure to polychlorinated biphenyl (PCBs) residues, organochlorine pesticides, and methylmercury with PD. The hypothesis is that increased exposure to these compounds will be associated with an increased risk of PD. Exposure will be determined by direct measurement of serum levels, as these compounds are persistent in body tissues. In addition, lifelong exposure will be estimated by structured interviews, including a dietary history with specific attention to intake of fish, marine mammals and wild game, known sources of bioconcentration of these environmentally persistent compounds. The project is being conducted in two phases. Phase 1 was a developmental period and is complete for study conduct in Anchorage. The specific aspects of the study design were established, detailed protocols were developed, and the necessary Institutional Review Board (IRB) approvals for the research were obtained. Phase 2, conduct of the case-control study, is now in progress.

B. Body

SCOPE OF WORK - PHASE 1

Task 1: Develop an ascertainment protocol using Indian Health Service (IHS) provider databases as the primary source, and identifying other possible sources of cases.
Task 2: Develop methods for identifying matched controls.
Accomplishments:
Approved methods were utilized to identify cases and controls for recruitment at the Alaska Native Medical Center (ANMC) in Anchorage during the past study period.

Task 3: Develop a preliminary proposal for review by Alaska Native leaders. Subsequent detailed versions of the study protocol will be submitted for review in accordance with protocol.
Accomplishments:
The study protocol, data collection instruments, and informed consents were submitted and approved by all necessary regulatory boards and the Human Research Protection Office (HRPO) Office of Research Protections (ORP) U.S. Army Medical Research and Materiel Command (USAMRMC) for study conduct at ANMC. The approved documents are being utilized to recruit, enroll, and collect data from study participants. Additional revisions to the protocol were submitted to the AK Area IRB November 25, 2008. There was no communication from the AK area IRB until October of 2009 when we were told by the AK Area IRB to reformat our submission and resubmit. We reformatted our review request and anticipate the revisions will be reviewed by the AK Area IRB in May 2010. If approved by all IRBs, tribal boards, and HRPO ORP USAMRMC, the revisions will allow for the consent of case subjects using a Legally Authorized Representative.

Task 4: Establishing appropriate infrastructure and personnel in Alaska. This will include a physician/neurologist, project manager, and local contacts within each tribal group. In addition, preliminary training in epidemiologic research methods may be a necessary part of a feasibility assessment.
Accomplishments:
Dr. Trimble, our local neurologist, has been involved with the project since its inception. In April 2007 we hired an Alaska based project manager, Amy Wiita. In May 2008 we hired Robin Morales, a

research assistant to conduct recruitment and data collection. All members of the research team completed human subjects training and training in study specific data collection methods.

Task 5: Develop study instruments and a detailed protocol.
Accomplishments:
Drafts were completed during year 2. We developed a study protocol and study instruments for collecting detailed life histories with special focus on exposures through diet, place of residence, and occupational exposures. After receiving approval from all review boards, the HRPO ORP USAMRMC requested additional changes to the protocol. Those changes were implemented, resubmitted, and approved. Study activities are being conducted under the current approvals.

We anticipate the need for additional detailed protocols if the pending submission for the consent of case subjects using a Legally Authorized Representative is approved by the AK area IRB, all other IRBs, tribal boards, and HRPO ORP USAMRMC.

Task 6: Refining the study protocol and preparing the operations manual.
Accomplishments:
The study protocol was refined and approved for use in Anchorage. The operations manual has been prepared. This manual will be updated if the pending submission for the consent of case subjects using a Legally Authorized Representative is approved.

Task 7: IRB approval of final protocols.
Accomplishments:
IRB approval to recruit in the ANMC in Anchorage was achieved January 16, 2008, and the study has been initiated in Anchorage (see Table 1). Additional revisions which would expand the eligible case population were submitted to the AK Area IRB November 2008 and are still pending final review (See above).

At the time of our last annual progress report, April 2009, we expected review of the protocol amendments in a short period of time and had therefore not submitted to the other regions of AK to seek regional tribal board approval. Because we continued to wait for AK Area IRB review of the revisions, in September 2009, we submitted the currently approved protocol and participant materials to all 10 regional tribal boards. The reviews of the currently approved protocol are underway or pending at each of the 10 tribal boards (Table 3).

Table 1. Human Subject Approval Status

Institution	Review Board	Status
Parkinson's Institute	Western IRB	Approved
Alaska Native Medical Center	AK Area IRB	Approved
Pacific Health Research Institute	VA Pacific Islands Health Care System	Approved
University of California San Francisco	UCSF Committee on Human Research	Approved
USAMRMC	Office of Research Protections	Approved

Table 2. Anchorage Service Unit Tribal Health Boards

Institution	Review Board	Status
Alaska Native Medical Center	AK Native Tribal Health Consortium	Approved
Alaska Native Medical Center	SouthCentral Foundation	Approved

Table 3. Regional Tribal Health Boards (regions outside the Anchorage service unit)

Region Served	Review Board	Submission Status	Approval
Kotzbue	Maniilaq Association	Review pending	pending
Sitka, Juneau, Klawok	Southeast AK Regional Health Consortium	Review pending	pending
Fairbanks	Tanana Chiefs Council	Review pending	pending
Nome	Norton Sound Health Corporation	Review complete	pending
Bethel	Yukon Kuskokwim Health Corporation	Review complete	pending
Kodiak	Kodiak Area Native Association	Review pending	pending
Dillingham	Bristol Bay Area Health Corporation	Review pending	pending
Barrow	Arctic Slope Native Association	Review pending	pending
Ketchikan	Ketchikan Indian Community	Review pending	pending
Metlakatla	Metlakatla Indian Community	Review pending	pending

SCOPE OF WORK - PHASE 2

Phase 2 was initiated in February 2008.
The goals of this phase are:

Task1: Identify approximately 50 cases of PD and 150 age matched participants without PD among the Native population in Alaska. This will be accomplished by working through tribal leaders, local health care providers and local contacts at the IHS to assist with identifying the most efficient and appropriate means of identifying cases and controls. Specifically, we will request assistance with gaining access to the IHS computerized medical record, the IHS hospital discharge data system, and pharmacy databases. These databases will be used to identify individuals with a diagnosis of PD and individuals on PD medications. Potential participants will be contacted by phone and administered a PD screening instrument. Those who agree to participate and who screen positively will be examined by a trained physician who will use standardized instruments for assessing Parkinson's disease (Unified Parkinson's Disease Rating Scale, Hoehn and Yahr stage, etc.). Participants will be videotaped to allow expert confirmation of diagnosis. Control participants will be selected from the same population and similarly screened.
Accomplished:
Cases: We established a list of 10 International Classification of Disease (ICD-9) codes related to PD. The patient database at the ANMC is periodically searched for these 10 codes. The electronic output from the searches is compiled by Dr. Trimble to identify suspect cases for screening. To date, we have generated a list of 80 potential cases of interest statewide.

To date, a total of 68 participants were screened and 41 participants completed all parts of the study at the AK Native Medical Center (ANMC).

19 potential cases screened at ANMC
- 2 Enrollment in progress
- 12 provided informed consent and are enrolled
  - 9 finished all parts of interview
  - 3 evaluations / interviews in progress
- 2 refusals
- 1 ineligible (death prior to enrollment)
- 2 on hold

49 potential controls screened at ANMC
- 0 Enrollment in progress
- 33 provided informed consent and are enrolled
  - 32 have finished all parts of interview
  - 1 interview in progress
- 2 refusals
- 6 ineligible
- 8 on hold

Task 2: Draw blood from cases and controls to measure levels of PCBs, organochlorine pesticides and methyl mercury.
Accomplished:
Ongoing training is conducted to ensure the proper collection, shipment, and processing of blood samples. We established a network of ANMC clinic phlebotomists to be on-call for study blood draws and update this as needed when ANMC staffing changes occur. After labeling, the blood samples are shipped overnight to the Parkinson's Institute laboratory for processing and storage. To date, samples from 43 subjects have been collected, shipped, and processed.

Task 3: Administer a structured interview to cases and controls to identify information important to the characterization of PCB, organochlorine pesticides and methyl mercury exposure (life time diet, occupation, place of residence, recreational activities) or identifying potential confounders (smoking cigarettes, drinking coffee, alcohol).
Accomplished:
Of the 45 subjects enrolled to date, 41 interviews have been completed and 4 are in-progress.

Task 4. Estimate logistic regression models adjusted for age and other potential confounders to determine the odds of PD among those with high levels of PCB , organochlorine pesticides and methyl mercury exposure, individually and in combination, relative to the odds of PD among those with no or low levels of exposure the toxicants.
Accomplished:
This step will not be initiated until all data collection is complete.

C. Key Research Accomplishments

- Held bi-monthly, face-to-face meetings with collaborators in AK to discuss study progress, challenges, and potential refinement to methods of case ascertainment.
- While study activities continue under the approved protocol, proposed revisions to the protocol were made and submitted to the AK Area IRB November 25, 2008. In October of 2009, we were told by the AK Area IRB to reformat our submission and resubmit. We reformatted our review request and anticipate the revisions will be reviewed by the AK Area IRB in May 2010. If approved by all IRBs, tribal boards, and HRPO ORP USAMRMC, the revisions will allow for the consent of case subjects using a Legally Authorized Representative which will expand our pool of eligible case enrollees.
- Case ascertainment, review of potential case medical records by Dr. Trimble, enrollment and data collection continued at the ANMC.
- Presented an in-person overview of the study to 4 of the 10 regional tribal boards to gain support and momentum for the approval process to facilitate statewide data collection.
- Submitted the approved protocol and study materials to the 10 regional tribal boards outside of the Anchorage service unit. We are in the process of addressing questions and concerns of each tribal board as they complete their reviews.
- Requested and received a no-cost extension of the project through April 2011.

D. Reportable Outcomes

We will not have reportable outcomes until all data collection is finished statewide.

E. Conclusions

Following the completion of subject enrollment, data and sample collection, and analysis, it will be possible to draw relevant scientific conclusions.

F. References
None

G. Appendices
None